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学位論文題目	Improvement of transdermal delivery of sumatriptan succinate using novel water emulsion patch or self-dissolving microneedle array, and their *in vitro* and *in vivo* characterizations （新規エマルションパッチ及び溶解型マイクロニードルを用いたスマトリプタンの経皮吸収性の改善ならびにこれら製剤の *in vitro* 及び *in vivo* における特性に関する研究）
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論文内容の要旨

Sumatriptan succinate (SS), a selective serotonin 5-hydroxytryptamine (5-HT) agonist at the 5-HT_{1B} and 5-HT_{1D} receptors, is the most frequently prescribed migraine therapy among a class of drugs known collectively as the triptans. SS has been commercialized for administration by oral, nasal spray and subcutaneous injection. Unfortunately, these formulations are associated with variety of limitations that can lead to patients' delay or avoid treatment. For example, the difficulty in taking an oral medication due to the nausea and vomiting that often accompany migraine, and the low bioavailability of oral and nasal spray (15% and 17%, respectively), as well as the skin site reactions and the reluctance of self-injection associated with subcutaneous injection. Therefore, in order to suppress those limitations while sustaining the therapeutic efficacy of SS, an alternative more effective SS delivery method is necessary for anti-migraine therapeutics. Transdermal drug delivery allows the permeation of drugs across the skin and enters into the systemic circulation, thus avoiding degradation by the gastrointestinal tract and hepatic first-pass metabolism. This delivery system is considered to be user-friendly, and is convenient administration. However, its application is limited to only a few hydrophobic low molecular compounds because of the outermost skin barrier layer, stratum corneum. In particular, SS has high hydrophilicity ($\log P_{pH\,7.4} = -0.86$) and it is difficult to pass through the skin barrier.

Based on these observations, in this study, I attempted to investigate two types of methodologies to improve the transdermal delivery of SS, including SS-incorporated passive patch and SS-loaded microneedle array (MN). An acrylic polymer emulsion, pressure sensitive adhesive Nikasol was chosen to prepare the SS-incorporated patch, and compared with a hydrophilic acrylic adhesive HGA. On the other hand, a novel self-dissolving MN was fabricated by employing sodium hyaluronate as the basic material. Various parameters such as needle lengths, thickness, and density as well as penetration enhancers were evaluated to enhance *in vitro* skin permeation of SS from MNs. Furthermore, the *in vivo* efficacy of the SS-loaded MNs for transdermal delivery of SS was characterized.

1. Development of a transdermal water emulsion patch system incorporating SS

Two types of transdermal patches containing SS were prepared, using either water emulsion resin Nikasol (SS Nikasol patch) or hydrophilic acrylic adhesive HGA (SS HGA patch). The contents of SS in both formulations were 20% (w/w). The thickness of all patches used ranged from 40 to 45 μm. *In vitro* permeated studies showed that the permeability of SS from the Nikasol patch was greater than that of the HGA patch, making it an excellent candidate for the development of SS transdermal patches. It was also found that SS permeation from the Nikasol patch was lower in humans, as compared to rats. An increase in transepidermal water loss was observed after application of both types of patches, however, this parameter gradually recovered to baseline, suggesting that the skin barrier disruption was reversible. No visible irritation appeared after application of the transdermal patches to rat skin during the experimental period. Furthermore, *in vivo* pharmacokinetic studies indicated that the absorption of SS from Nikasol patch was significantly higher than that of the HGA patch, which was well consistent with the *in vitro* skin permeation results. In addition, SS was effectively absorbed from Nikasol patch through the skin and associated with relatively greater absolute bioavailability than that of oral administration, achieving a consistent plasma concentration over an extended period of time. These findings demonstrated that the novel patch system fabricated from emulsion Nikasol was a useful and promising alternative method to improve transdermal delivery of SS without any serious skin damage.

2. Development of a novel self-dissolving MN loaded with SS

SS-loaded MNs with different needle length, thickness, density and penetration enhancers were fabricated from sodium hyaluronate. All the needles were tapered cone-shaped in a circular array with a diameter of 10 mm. MNs with the length of 800 μm could effectively improve the transdermal permeability of SS compared with that of 500 μm. No distinct enhancement was obtained by increasing the thickness of MNs or by adding penetration enhancers in the prescription of MNs. Further, skin permeability of SS could significantly improve after increasing needle numbers. Therefore, high density MNs with needle length of 800 μm were chosen for the subsequent studies.

The resulting SS-loaded MNs possessed sufficient mechanical strength to successfully puncture the skin barrier and maintained their skin piercing abilities for at least 30 min after being placed at a high relative humidity of 75%. Optical coherence tomography images demonstrated that the MNs uniformly created drug permeation pathways after being inserted into the skin. Almost all of the formulated SS was released from the MNs at a relatively constant rate within 1 h via an *in vitro* release study. It was also noted that needles began to dissolve upon application onto rat skin *in vivo* and were completely dissolved within 1 h. These findings suggested that the novel MNs had biocompatible properties and SS appeared to be rapidly released from these MNs. Moreover, MNs significantly increased transepidermal water loss; however, skin barrier function gradually recovered to control levels within 24 h, in contrast to the skin damage observed after tape stripping treatment. These findings indicated that the micro-scale pathways created by the microneedles quickly resealed, and that the skin damage was reversible, which were highly consistent with the rapidly recovery of micropores created by insertion of blue dye contained MNs into rat skin. Furthermore, a dose-dependent plasma concentration of SS was obtained after treatment with SS-loaded MNs in rats. Pharmacokinetic characteristics indicated that absorption of SS delivered by MNs was similar to that observed after subcutaneous injection and was associated with high bioavailability (~90%), which was much higher than that produced by oral administration. These findings suggested that application of SS-loaded MNs to the skin provided an effective alternative approach to enhance the transdermal delivery of SS without serious skin damage, while avoiding the pain caused by usage of hypodermic needles.

In conclusion, the present findings indicated that both the water emulsion patch choosing Nikasol as an adhesive and the self-dissolving MN fabricated from sodium hyaluronate were useful and promising alternative approaches to improve transdermal delivery of SS without serious skin damage. Further, the novel MN seems to be a much more effective method in clinical application due to the reasonable administration size and rapid onset of action, would be likely to improve patient compliance.

審 査 の 結 果 の 要 旨

スマトリプタンは、セロトニンの選択的なアゴニストであり、片頭痛の治療薬として臨床応用されている薬物である。現在、スマトリプタンの投与経路は経口、経鼻スプレー、皮下注射により投与されているが、これら投与経路によるスマトリプタンの投与にはいくつかの欠点があることが知られている。すなわち、スマトリプタンの経口投与は、肝臓で初回通過効果を受けるため、バイオアベイラビリティが低く、なおかつ吐き気、嘔吐などの副作用がみられる。また、スマトリプタンの経鼻投与後のバイオアベイラビリティは17%程度と比較的高いが、鼻やのどなどに刺激を伴うことが知られている。一方、スマトリプタンの皮下投与は即効性がみられるが、注射による痛みを伴い、副作用も発現しやすいことが欠点となる。そこで、本研究では、スマトリプタンの新たな投与経路として、経皮投与に着目した。

一般に、皮膚の最外層には角質層が存在し、薬物透過の最大の透過障壁となるため、水溶性や高分子薬物の透過が制限されている。したがって、薬物の経皮適用を可能にするためには、薬物の皮膚透過性を改善する必要がある。こうした観点から、現在までに経皮吸収促進剤の利用、プロドラッグ化修飾、イオントフォレシスの利用、ソノフォレシスの利用などの様々な経皮吸収改善方法が試みられているが、本研究ではパッチ製剤とマイクロニードルを用いて、スマトリプタンの経皮吸収性の改善を試みた。

まず、新規エマルションパッチ製剤であるNikasolパッチ製剤を用いてスマトリプタンの経皮吸収性を評価したところ、*in vitro* 透過実験において、従来のパッチ製剤に比較してスマトリプタンの高い皮膚透過性が観察され、皮膚刺激性などもあまり観察されなかった。また、*in vivo* 吸収実験においてもスマトリプタンの経皮吸収性は、Nikasolパッチ製剤を用いることにより経口投与に比べ増大することが認められた。

一方、マイクロニードル製剤としては、自己溶解型であり、生体分解性であるヒアルロン酸を素材としたマイクロニードルにスマトリプタンを封入し、皮膚に適用したところ、きわめて高い皮膚透過性や経皮吸収性が得られた。特に、*in vivo* 吸収実験においては皮下投与に匹敵する血漿中濃度が得られた。さらに、マイクロニードル適用時の水分蒸散量 (Transepidermal water loss, TEWL) は一時的に上昇するが、可逆的であり、一定時間後に回復したことから、マイクロニードルがきわめて安全性の高い製剤であることが実証された。

以上のことから、Nikasolパッチ製剤及びマイクロニードル製剤は、片頭痛治療薬であるスマトリプタンの経皮吸収改善に有効であることが認められた。特に、後者のマイクロニードル製剤はスマトリプタンの経皮吸収性を顕著に改善し、安全性にも優れていることから、今後、有効かつ安全性の高い経皮適用製剤としての臨床応用が期待される。

学位論文とその基礎となる報文の内容を審査した結果、本論文は博士（薬科学）の学位論文としての価値を有するものと判断する。